SUMMARY OF DATA FOR CHEMICAL SELECTION

5-Amino-*o*-cresol

2835-95-2

BASIS OF NOMINATION TO THE CSWG

5-Amino-*o*-cresol is brought to the attention of the CSWG because it is the most widely used member of a class of 25 chemicals, the aminocresols and related compounds, defined as amino- and methyl-substituted phenols, their salts, and ethers. Prior to conducting the class study, the NCI had submitted seven aminocresols, including 5-amino-*o*-cresol, to be tested for genotoxicity in the NCI Short-Term Test Program (STTP). Nearly all produced positive results in either the Ames *Salmonella typhimurium* assay for mutagenicity, the mouse lymphoma assay for clastogenicity, or both. These results warrant investigation of the carcinogenic potential of the class members with the highest production volume and potential exposure.

5-Amino-*o*-cresol is used as an oxidative dye coupler in cosmetic hair dye manufacturing. According to the US Environmental Protection Agency (EPA), the annual production level of 5-amino-*o*-cresol is 10,000 to 100,000 lbs. According to a National Institute for Occupational Safety and Health (NIOSH) survey conducted in 1981 - 1983, approximately 45,000 workers are exposed to 5-amino-*o*-cresol; however, no permissible exposure limit (PEL) has been established to regulate worker exposure to this compound. Use of this compound in hair dye production also leads to widespread occupational and consumer exposure.

Suspicion of carcinogenic potential of 5-amino-*o*-cresol is based primarily on its genotoxicity and subchronic toxicity, as well as some equivocal epidemiologic evidence of carcinogenic potential of some hair dye formulations.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker of the EPA provided information on the annual production volume of 5-amino-*o*-cresol.

SELECTION STATUS

Action BY CSWG: 7/26/01

Studies requested:

- Metabolism
- Developmental and Reproductive Toxicity
- Carcinogenicity

Priority: High

Rationale/Remarks:

- Most widely used member of the aminocresols class of chemicals
- Suspicion of carcinogenicity based on results of short-term tests of several aminocresols
- Lack of information on carcinogenicity of the aminocresols class of chemicals
- Hairdressers and consumers who use certain hair dyes potentially exposed; substance passes through skin in small but detectable amounts
- Consider skin painting, possibly using the TGAC mouse as a model

CHEMICAL IDENTIFICATION

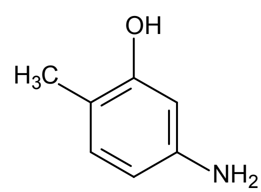
CAS Registry Number: 2835-95-2

CAS Name: Phenol, 5-amino-2-methyl (9CI)

Synonyms and Trade Names: 5-Amino-*o*-cresol; 5-amino-2-methylphenol; 2-methyl-5-aminophenol; 4-amino-2-hydroxytoluene; 2-hydroxy-4-aminotoluene; 4-amino-2-hydroxy-1-methylbenzene; 2-hydroxy-*p*-toluidine; 3-hydroxy-4-methylaniline; 3-amino-6-methylphenol; 6-methyl-3-aminophenol

Structural Class: Substituted phenol

Structure, Molecular Formula, and Molecular Weight:



C_7H_9NO Mol. wt.: 123.17

Chemical and Physical Properties:

Description: Light brown powder (CIR Expert Panel, 1989)

Melting Point: 160-175°C (sublimes) (Penn Bio-Organics, 2001; Oxford, 2001)

Solubility: Insoluble in water, soluble in organic solvents (CIR Expert Panel, 1989)

Reactivity: Stable under normal conditions; reacts with oxidizing agents (CIR Expert Panel, 1989)

O/W Partition Coefficient: log $K_{O/W}$ = 25.4 (CIR Expert Panel, 1989)

Technical Products and Impurities: 5-Amino-*o*-cresol is available from TCI America and Sigma-Aldrich at greater than 97% purity (Sigma-Aldrich, 2001; TCI America, 2001).

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EXPOSURE INFORMATION

Production and Producers:

Manufacturing Process. No information on the manufacturing process for 5-amino-*o*-cresol was found in the available literature.

Production/Import Level. 5-Amino-*o*-cresol is listed in the EPA's Toxic Substances Control Act (TSCA) Chemical Inventory (NLM, 1999). According to the EPA data, the annual production volume of 5-amino-*o*-cresol is between 10 and 100 thousand pounds (Walker, 2001).

Chemical Sources International (2001) lists 11 producers of 5-amino-*o*-cresol, including 7 in the US. The Directory of World Chemical Producers (DWCP, 2000) lists two European and one Japanese producer of the compound. Chemcyclopedia (2001) lists one Japanese producer of 5-amino-*o*-cresol.

Producers and Importers: The search of the available literature has identified one US manufacturer of 5-amino-*o*-cresol on a laboratory scale, GL Synthesis, Inc. (GL Synthesis, 2001). 5-Amino-*o*-cresol is distributed in the US by five suppliers: Biddle Sawyer Corp., GL Synthesis, Inc., Penn Bio-Organics, Sigma-Aldrich, TCI America (GL Synthesis, 2001; Hunter, 2000; Penn Bio-Organics, 2001; TCI America, 2001; Tilton, 2000).

Use Pattern: 5-Amino-*o*-cresol is used almost exclusively in the cosmetic industry as a coupler (secondary intermediate) in oxidative (permanent) hair dye formulations, which produce hair coloration that lasts until the hair grows out. Color is formed inside the hair by hydrogen peroxide-induced coupling reactions of colorless dye precursors. Color-forming reactions are accomplished by primary intermediates, secondary intermediates, and oxidants. The amounts and chemical structures of these precursors, as well as the pH at which the process takes place and the dyeing time, determine the resultant color. The primary intermediates include the so-called para dyes, *p*-phenylenediamine, *p*-

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toluenediamine, *p*-aminodiphenylamine, and *p*-aminophenol, which form a quinone monoimine or diimine upon oxidation. The secondary intermediates, or couplers, include *m*-diamines, *m*-aminophenols (including 5-amino-*o*-cresol), polyhydroxyphenols, and naphthols. For example, the reaction of 5-amino-*o*-cresol with *p*-phenylenediamine produces a red-violet color; its reaction with *p*-aminophenol produces an orange-red color. The color of a mixture cannot readily be predicted and involves trial and error. The colorant formulation is mixed with an oxidizing agent (developer) just before application. The preferred developer is usually a 6% solution of hydrogen peroxide, which also bleaches the hair, allowing the development of lighter colors (Akerson *et al*., 1994; Brown *et al*., 1985; CIR Expert Panel, 1989; Wenke & Prota, 1999).

In 1986, 5-amino-*o*-cresol was used in 149 out of 960 hair dye formulations, according to the FDA product formulation data, compiled through voluntary filing in accordance with Title 21 of the Code of Federal Regulations. Six products contained greater than 1 – 5% 5-amino-*o*-cresol, 70 products contained greater than 0.1 – 1%, and 73 products contained 0.1% or less. 5-Amino-*o*-cresol is reported as one of the more reactive couplers with respect to its reactivity towards monoimines (CIR Expert Panel, 1989).

The United States Patent and Trademark Office (USPTO, 2001) listed 55 patent citations for 5-amino-*o*-cresol; 27 under the synonym, 4-amino-2-hydroxytoluene; and 107 under the synonym, 5-amino-2-methylphenol.

<u>Human Exposure</u>: The primary route of exposure to 5-amino-*o*-cresol is through dermal contact. Limited data are available on the extent of specific exposure to 5-amino-*o*-cresol. However, some information on human exposure to hair dyes will be discussed here.

Occupational Exposure. National Occupational Exposure Survey (NOES), conducted by the National Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 44,842 employees, including 35,032 female employees, were potentially exposed to 5-amino-*o*-cresol in the workplace (NLM, 1999).

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According to the Bureau of Labor Statistics (BLS) National Industry-Occupation Employment Matrix, total employment for hairdressers, hairstylists, and cosmetologists was 605,165 in 1998. The projected employment for 2008 is 666,969, which represents an increase of 61,804, or 10.2% (Frank, 1999).

Environmental Exposure. No information on environmental exposure to 5-amino-*o*-cresol was found in the available literature.

Consumer Exposure. Consumer exposure to 5-amino-*o*-cresol occurs through the use of hair coloring cosmetic products. Hair coloring preparations have been in use since the ancient Egyptians, and recorded recipes, involving plant extracts or metallic dyes, exist in many cultures. In the latter part of the 19th century, synthetic organic compounds were discovered which eventually led to modern hair coloring (Akerson *et al*., 1994).

While women have traditionally constituted the majority of hair dye users, hair coloring among men has also been on the rise in the recent years. According to a report by a CNN senior writer, men spent an estimated $129.9 million in 1999 on hair-coloring products. Sales of these products have more than tripled in the last decade, and advertising has doubled in the same period (Keller, 2000).

According to the estimates reported in the University of Southern California (USC) hair dye study, throughout Europe, North America, and Japan, one in three women above the age of 18 and one in ten men above the age of 40 use some type of hair coloring. Permanent coloring accounts for approximately 75% of the global hair dye use (Weiner, 2001). Estimates provided by the Cancer Information Service (CIS) suggest that current hair dye usage in the US ranges from 20 to 60 percent of the population (CIS, 2001), while the Cosmetic, Toiletry, and Fragrance Association (CTFA) estimates that close to two out of every five American women and a smaller number of men dye their hair (Patlak, 1993).

Environmental Occurrence: No information on the environmental occurrence of 5-amino-*o*-cresol was found in the available literature.

Regulatory Status: Hair dyes and hair dye ingredients are regulated as cosmetic products by the US Food and Drug Administration (FDA). Cosmetics produced or distributed for retail sale to consumers for their personal care are required to bear an ingredient declaration. Hair preparations used by professionals at their establishments and places of work are exempt from this requirement provided that these products are not sold to consumers for home use (FDA, 2001).

The FDA restricts the potential use of certain color additives under the Federal Food, Drug, and Cosmetic (FD&C) Act. These restrictions are contained in the Code of Federal Regulations, 21 CFR 73 and 74 (Akerson *et al*., 1994).

Under the FD&C Act, the FDA does not have authority to require premarket approval for cosmetics, but it can take action when safety issues surface (Meadows, 2001).

No specific regulatory information for 5-amino-*o*-cresol was found in the available literature.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: In a modified Draize repeat insult patch test (RIPT) two aqueous solutions (3% v/v and 10% w/v) of a 2% 5-amino-*o*-cresol were administered to volunteers. A dose-related increase in dermatitis was observed (1 of 23, not reproduced, vs. 2 of 31, 1 reproduced on rechallenge) (CIR Expert Panel, 1989).

Hair dye use has been evaluated in a number of cohort studies for its possible association with cancer. In 1993, the International Agency for Research on Cancer (IARC) evaluated six European studies of male hairdressers and barbers, some showing an increase in urinary bladder tumors. IARC concluded that occupation as a hairdresser or barber entails exposures that are probably carcinogenic. However, linkage between personal use of hair dyes and cancer could not be evaluated (IARC, 1993). Other studies, which investigated association between permanent hair dye use and breast and hematopoietic cancers, yielded largely negative results (Altekruse *et al*., 1999; Kinlen *et al*., 1977; Koenig *et al*., 1981).

Two recent case-control studies conducted in California (Gago-Dominguez *et al*., 2001) and Nebraska (Zahm *et al*., 1992) showed some linkage between permanent hair dye use and cancer incidence. Interestingly, the latter study found that the risks were higher among women who used brown, black, or red hair dyes, i.e., colors whose preparation may involve 5-amino-*o*-cresol (CIR Expert Panel, 1989; Akerson *et al*., 1994). It must be noted, however, that none of the epidemiological studies found in the available literature discussed the specific ingredients (such as 5-amino-*o*-cresol) contained in the hair dyes.

Animal Data:

Carcinogenesis Studies. No two-year carcinogenicity studies of 5-amino-*o*-cresol were found in the available literature.

Skin painting studies of hair dyes containing 5-amino-*o*-cresol were negative (CIR Expert Panel, 1989)

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Acute Studies. 5-Amino-*o*-cresol has been described as non-irritating to the skin and mildly irritating to the eye, based on tests in rabbits (Lloyd *et al*., 1977).

In two skin sensitization tests in guinea pigs, 5-amino-*o*-cresol produced weak sensitization (CIR Expert Panel, 1989).

The acute toxicity values reported for 5-amino-*o*-cresol are presented in Table 1.

Table 1. Acute toxicity values for 5-amino-*o*-cresol.

Route	Species	LD_{50} (mg/kg)	Reference
Oral	Rat, female	2928	CIR Expert Panel, 1989
	Rat, male	4355	CIR Expert Panel, 1989
	Rat	3600	Lloyd *et al*., 1977
	Quail	750	NLM, 1999
	Sparrow	562	CIR Expert Panel, 1989
	Blackbird	> 1000	CIR Expert Panel, 1989
	Starling	> 1000	CIR Expert Panel, 1989
Dermal	Rabbit	> 5000	NLM, 1999

Subchronic Studies. The CTFA commissioned a subchronic study of 5-amino-*o*-cresol in groups of 40 male and 35 female Sprague-Dawley rats. Blood was collected from 5 males and 5 females of the control and high-dose groups at 6 wk for methemoglobin, tri-iodothyronine, and tetraiodothyronine testing. At 13 wk, 10 males and 10 females from each group were killed, and the blood was collected for hematology and clinical chemistry tests. All the major organs from the control and high-dose groups, as well livers, kidneys, bladders, thyroids, and gross lesions from the low- and mid-dose groups, were examined microscopically (CIR Expert Panel, 1989). The summary of the subchronic study protocol is presented in Table 2.

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Table 2. The subchronic study of 5-amino-*o*-cresol in Sprague-Dawley rats.

Sex	Number of Animals	Dose (% in Diet)	Exposure Time (wk)	Recovery Time (wk)	Histopathology
Male	10 10 10 10	0.0 0.3 1.0 3.0	13	None	All organs Selected organs* Selected organs Yes
Male	10 10 10 10	0.0 0.3 1.0 3.0	26	None	Liver, thyroid Thyroid Thyroid Liver, thyroid
Male	20 20 20 20	0.0 0.3 1.0 3.0	20	6	Thyroid Thyroid Thyroid Thyroid
Female	10 10 10 10	0.0 0.3 1.0 3.0	13	None	All organs Selected organs Selected organs All organs
Female	15 15 15 15	0.0 0.3 1.0 3.0	13	None	Liver, thyroid Thyroid Thyroid Liver, thyroid
Female	10 10 10 10	0.0 0.3 1.0 3.0	26	None	Liver, thyroid Thyroid Thyroid Liver, thyroid

*Liver, kidneys, urinary bladder, thyroid, and gross lesions.
Source: CIR Expert Panel, 1989.

No significant differences were noted between the concentrations of methemoglobin and triiodothyronine in the high-dose and control rats. Tetraiodothyronine levels and the free thyroxine index were significantly decreased in the high-dose rats, which was indicative of a hypothyroid state. That conclusion was further supported by enlarged thyroids exhibited by the mid- and high-dose animals. The increased cholesterol levels in the high- and mid-dose groups were also attributed to the hypothyroid state (CIR Expert Panel, 1989).

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Thyroids of the high- and mid-dose rats showed moderate follicular cell hyperplasia and misshapen and small follicles. This condition was characterized as a sporadic micro-follicular goiter and was attributed to an increase in the cell size of the epithelium surrounding the follicles. At the end of the 26-wk study, the tetraiodothyronine levels were increased in the high- and mid-dose animals, including those that underwent a 6-week recovery period. The thyroids of all high-dose rats exhibited sporadic microfollicular goiter lesions similar to those seen at 13 weeks, and one animal had a small follicular cell adenoma of the thyroid (CIR Expert Panel, 1989).

Significant dose-dependent decreases in erythrocyte count, hemoglobin, and hematocrit were observed in female rats. High-dose males and females had significant increases in the mean corpuscular volume. These observations were suggestive of anemia and may have been related to nutritional deficiency (CIR Expert Panel, 1989).

Exposure to 5-amino-*o*-cresol also produced significant hepatotoxic effects, manifested in centrilobular hepatocytomegaly of the liver in unspecified number of test rats and one control female. Mid- and high-dose male rats exhibited a significant dose-dependent increase in the serum pyruvic transaminase activity (CIR Expert Panel, 1989).

<u>Short-Term Tests</u>: Mutagenicity tests of 5-amino-*o*-cresol have produced contradictory results. The results of these tests are summarized in Table 3.

In a study on genotoxicity of commercial hair dye preparations, human volunteers (6 females and 4 males per group) had their hair dyed 13 times at intervals of 3 – 6 wk and their lymphocytes tested for chromosomal aberrations (CA) and sister chromatid exchanges (SCE). All of the preparations used, including those that contained 5-amino-*o*-cresol, tested negative for both CA and SCE (Hofer *et al*., 1983; Turanitz *et al*., 1983).

Table 3. Mutagenicity data on 5-amino-*o*-cresol.

Test	Organism/Strain(s)	Dose	Metabolic Activation	Results	Reference
Ames	*Salmonella* TA98	15 – 150 µg/plate	± S-9	(–)	CIR Expert Panel, 1989
Ames	*Salmonella* TA97, TA98, TA100, TA1535	33 – 3333 µg/plate	± S-9	(+)	Zeiger *et al*., 1988
Ames	*Salmonella* TA98, TA100, TA102, TA1535, TA1537	100 – 10,000 µg/plate	± S-9	(–)	NLM, 2001a
Micronucleus	Rat polychromatic erythrocytes	4000 mg/kg twice by intubation	*In vivo*	(–)	CIR Expert Panel, 1989
Micronucleus	Mammalian polychromatic erythrocytes	Not reported	Not reported	Inconclusive	NLM, 2001b
Chromosomal aberrations	Mammalian polychromatic erythrocytes	Not reported	Not reported	Inconclusive	NLM, 2001b

(+) = Positive; (–) = negative; ± = with or without.

Metabolism: According to the study by Beck and co-workers (1994), both pig skin (*in vitro*) and rat skin (*in vivo*) are permeable to 5-amino-*o*-cresol, the latter being more permeable.

Wolfram and Maibach (1985) studied percutaneous absorption of 5-amino-*o*-cresol in a hair dye under the conditions of usage. Radiolabeled 5-amino-*o*-cresol was added to a commercial dye containing 0.69% non-radioactive 5-amino-*o*-cresol; the mixture was applied to dry hair of three volunteers, worked into the hair mass for 5 – 8 min, and rinsed off after an additional 20 min; the urine samples were collected for as long as radioactivity was detected, for approximately 144 h. The total urinary excretion of radioactivity was 0.2% with 50% of that excreted in 24 h. A high recovery of radioactivity in urine was reported when 5-amino-*o*-cresol was administered to human volunteers orally (CIR Expert Panel, 1989).

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In hairless Wistar rats, of the applied dose of 5-amino-*o*-cresol (3.44 μM/cm^2 skin), 56.8 nM/cm^2 was found to penetrate the skin, of which 2/3 was excreted in the urine and 1/3 in the feces (CIR Expert Panel, 1989).

Other Biological Effects: The previously mentioned subchronic study of 5-amino-*o*-cresol included investigation of its teratogenic effects. Groups of 25 female rats were fed diets containing 0, 0.3, 1, or 3% 5-amino-*o*-cresol for 14 wk, then mated with untreated males. The feeding was resumed at the same doses for the duration of gestation. While no visceral malformations were noted, there was a significant increase in the number of rudimentary 14th ribs in the mid- and high-dose animals and a slight increase in the number of full 14th ribs in the fetuses of these dose groups (CIR Expert Panel, 1989).

In a dominant lethal study of 5-amino-*o*-cresol, 20 male rats from each dose group (see above) were removed from the test diet after 20 wk and mated to two untreated females each week for two weeks. All males, except one in the mid-dose group, sired at least one litter. No significant dose-related differences were noted in any of the reproductive parameters studied. The authors concluded that 5-amino-*o*-cresol produced no adverse effects on reproductive performance and no dominant lethal effect (CIR Expert Panel, 1989).

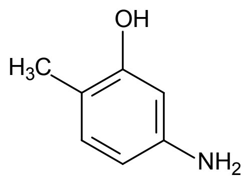
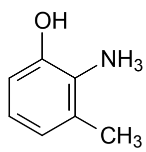
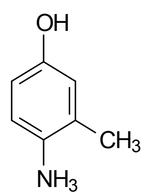
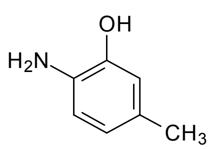
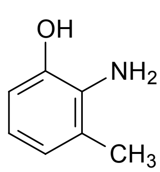
Structure/Activity Relationships: 5-Amino-*o*-cresol was selected for nomination to the CSWG from a class study of 10 aminocresols and 15 related salts and ethers. Nine aminocresols most closely related to 5-amino-*o*-cresol were selected for the present discussion. No relevant information for five of these substances (3-amino-*o*-cresol [53222-92-7]; 4-amino-*o*-cresol [2835-96-3]; 6-amino-*o*-cresol [17672-22-9]; 5-amino-*m*-cresol [76619-89-1]; and 3-amino-*p*-cresol [2836-00-2]) was found in the available sources.

For the remaining four aminocresols, the search of the available literature yielded mutagenicity data only. All four compounds were clastogenic in the mouse lymphoma assay, both with and without metabolic activation. 2-Amino-*m*-cresol [2835-97-4] and

4-amino-*m*-cresol [2835-99-6] produced negative results in the Ames *Salmonella typhimurium* mutagenicity assay with and without metabolic activation. 6-Amino-*m*-cresol [2835-98-5] was positive in the TA100 *Salmonella typhimurium* strain without metabolic activation. 2-Amino-*p*-cresol [95-84-1] was positive in TA97 (without activation) and TA100 (with and without activation) (NLM, 2001a).

The mutagenicity data for 5-amino-*o*-cresol and the four related compounds are summarized in Table 4.

Table 4. Summary of mutagenicity data on 5-amino-*o*-cresol and related compounds.

Compound	Mutagenicity Data
5-Amino-*o*-cresol [2835-95-2] 	Positive in *S. typhimurium* TA97, TA98, TA100 w S-9; negative in *S. typhimurium* TA1535 w/wo S-9 (Zeiger *et al*., 1988). Negative in *S. typhimurium* TA98, TA100, TA102, TA1535, TA1537 w/wo S-9 (NLM, 2001a, records pending) Equivocal in micronucleus test (CIR Expert Panel, 1989; NLM, 2001b). Equivocal in chromosomal aberration test (NLM, 2001b).
2-Amino-*m*-cresol [2835-97-4] 	Negative in *S. typhimurium* w/wo S-9 (NLM, 2001a). Positive in mouse lymphoma test w/wo S-9 (NLM, 2001a).
4-Amino-*m*-cresol [2835-99-6] 	Negative in *S. typhimurium* w/wo S-9 (NLM, 2001a). Positive in mouse lymphoma test wo S-9 (NLM, 2001a).
6-Amino-*m*-cresol [2835-98-5] 	Positive in *S. typhimurium* TA100 wo S-9 (NLM, 2001a). Positive in mouse lymphoma test w/wo S-9 (NLM, 2001a).
2-Amino-*p*-cresol [95-84-1] 	Positive in Ames TA97 wo S-9 and TA100 w/wo S-9 (NLM, 2001a). Positive in mouse lymphoma test w/wo S-9 (NLM, 2001a).

ND = no data found in the available literature; w/wo = with or without.

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